
Chromatin and transcriptional signatures for Nodal signaling during endoderm formation in hESCs.

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Public Summary:

Scientific Abstract:

The first stages of embryonic differentiation are driven by signaling pathways hardwired to induce particular fates. Endoderm commitment is controlled by the TGF-beta superfamily member, Nodal, which utilizes the transcription factors, SMAD2/3, SMAD4 and FOXH1, to drive target gene expression. While the role of Nodal is well defined within the context of endoderm commitment, mechanistically it is unknown how this signal interacts with chromatin on a genome wide scale to trigger downstream responses. To elucidate the Nodal transcriptional network that governs endoderm formation, we used ChIP-seq to identify genomic targets for SMAD2/3, SMAD3, SMAD4, FOXH1 and the active and repressive chromatin marks, H3K4me3 and H3K27me3, in human embryonic stem cells (hESCs) and derived endoderm. We demonstrate that while SMAD2/3, SMAD4 and FOXH1 associate with DNA in a highly dynamic fashion, there is an optimal bivalent signature at 32 gene loci for driving endoderm commitment. Initially, this signature is marked by both H3K4me3 and H3K27me3 as a very broad bivalent domain in hESCs. Within the first 24h, SMAD2/3 accumulation coincides with H3K27me3 reduction so that these loci become monovalent marked by H3K4me3. JMJD3, a histone demethylase, is simultaneously recruited to these promoters, suggesting a conservation of mechanism at multiple promoters genome-wide. The correlation between SMAD2/3 binding, monovalent formation and transcriptional activation suggests a mechanism by which SMAD proteins coordinate with chromatin at critical promoters to drive endoderm specification.

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